Remarks/Arguments

Claims 1-55 are pending in the present application, with claims 31-39, 51 and 53-55 being subject to examination.

Rejection under Section 112

Claim 33 has been rejected under Section 112 for reciting "substantially." Specifically. Claim 33 recites "The crystalline form of claim 32, wherein the crystalline form has an XRPD pattern as **substantially** depicted in Figure 25." (emphasis added).

The term "substantially" is definite and appropriate here because a curve based on data points is inherently and inevitably variable to some small degree, and one of ordinary skill in the art would know what "substantially as depicted in the curves" means. See, e.g., MPEP § 2173.05(b)(D); Andrew Corp. v. Gabriel Elecs., Inc., 847 F.2d 819, 821 (Fed. Cir. 1988) (holding a claim not indefinite for reciting an antenna "which produces *substantially equal* E and H plane illumination patterns") (courtesy copy enclosed — see Exhibit 1).

One of ordinary skill of art is aware that an XRD powder pattern may contain a certain degree experimental error. The error may result from a variety of factors, such as sample preparation, instrument calibration, impurities etc. Furthermore, the specification of the present invention does provide some quantification for errors at least for peak positions, that is ±0.2 degrees two theta.

At last, the Patent Office has issued numerous patents in which the term "substantial" is used in a claim to a powder XRD pattern. (*See e.g.* US Patent No. 7148376, claim 3; US Patent 7144916, claim 1). It is respectfully submitted that claim 33 meets all the requirements set forth under Section 112.

Rejection under Section 103

Claims 31-36, 51, 53-55 have been rejected under Section 103 over Sumikawa (US Patent 5,488,150). The Office Action states:

With respect to the lack of teaching nateglinide form ε, the prior art is silent. However, the prior art does offer guidance that the solid trans-4-isoproylcyclohexylcarbonyl)-D-phenylalanine compound suspended in suitable solvent may be of any type (see col. 5 ,lines 10-12), which does include the possible formation of nateglinide form ε during the prior art process. This is because the prior art process does use the claimed solvents such as acetone, acetonitrile in the claimed process(see col. 5, lines 20-27). Therefore, it would have been obvious to the skilled artisan in the art to be motivated to find the claimed nateglinide form ε by routine experimentation in the Sumikawa et al process. This is because the skilled artisan in the art would expect such a process to be successful and feasible due to the presence of the suitable claimed solvents in the Sumikawa et al process.

But Sumikawa does not teach or suggest nateglinide Form Epsilon or its existence, much less a process for its preparation with a reasonable expectation of success.
The Office Action states that Sumikawa could have possibly produced Form Epsilon. The Office Action does not analyze the XRPD patterns of the products of Sumikawa to determine if Sumikawa's product contained Form Epsilon.

Form Epsilon is not detectable in the powder obtained for Forms B and H in Sumikawa. According to the present specification, and as claimed, Form Epsilon has the following XRDP peaks: 4.2, 13.0, 13.6, 14.3, 16.2, 16.7 and 19.7 ± 0.2 degrees two theta. Figure 1 of Sumikawa, which discloses Form B, specifically lacks peaks, at 4.2, 13.0, 13.6, 19.7 ± 0.2 degrees two theta. Figure 3, of Sumikawa, which discloses Form H, specifically lacks a peak at 4.2, 13.6 and 16.7 ± 0.2 degrees two theta."

The use of XRPD to identify and distinguish polymorphs is the standard technique in the art:

> X-ray powder diffraction is perhaps the "gold standard" for the qualitative determination of crystallinity. Not only can the presence of a crystalline phase by confirmed, but since each

> polymorph produces a unique diffraction pattern, the question of which polymorph crystallized can be addressed.

Brittain, H.G., *Polymorphism in Pharmaceutical Solids* p. 398-99 (Marcel Dekkler 1999). Thus, since the XRPD patterns disclosed in Sumikawa do not show presence of Form Epsilon as claimed in the present invention, Sumikawa's process did not "possibly" produce Form Epsilon.

As the Examiner is aware, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Sumikawa at most provides a laundry list of solvents. The only claimed solvent used by Sumikawa in the examples is acetone, which is used in a mixture with water. Sumikawa does not teach that crystallization from acetone in the absence of water would result in Form Epsilon. The unpredictable nature of polymorph generation precludes a *prima facie* case of obviousness. The literature is replete with references attesting to the unpredictability of polymorphs. "Perhaps the chief challenge in managing the phenomenon of multiple solid forms of drug is our inability to predict how many forms can be expected in any given case." Byrn, *et al.*, "Solid-State Pharmaceutical Chemistry," *Chem. Mater.* 6, 1148-1158 (1994). For example, only recently was a second polymorph for aspirin found despite being first synthesized in 1853. Wishweshwar, *et al.*, *J. Am. Chem. Soc.*, 127, 16802-16803 (2005). The process of crystallization is affected by many physical parameters, and this element of predictability has serious implications for solids design in crystal engineering. M. Caira, (Crystalline Polymorphism of Organic Compounds," *Topics in Current Chemistry*, vol. 198, 164-208 (1998). "There's no way to tell what a large floppy molecule can do in the solid state except by doing experiments." M. Rouhi, "The Right Stuff," Chem. & Eng. News 32-

35 (2003). "Until that time [that computer programs are able to predict stable crystal forms] the development scientist is handicapped in attempting to predict how many solid forms of a drug are likely to be found." H.G. Brittain, "Polymorphism in Pharmaceutical Solids," p. 185 (Marcel Dekker 1999).

Therefore, the claimed Form Epsilon of the present invention and processes for its preparation are not obvious in view of the prior art due to unpredictable nature of polymorphism and the lack of teaching in Sumikawa for preparation of Form Epsilon..

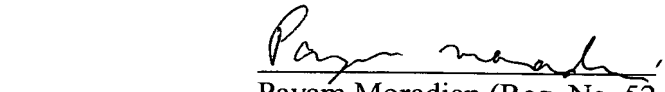
The Office Action rejects claims 31-39, 51, 53-55 and 79 in view of Sumikawa and further in view of Grant and Hackh's Chemical Dictionary. The dictionary is used for the proposition that nitromethane, a solvent that is absent in Sumikawa, is water soluble. The Office Action then takes the leap that because nitromethane is a water soluble solvent, one of ordinary skill of art would have been motivated to use it to prepare Form Epsilon. As stated above, Sumikawa does not teach or suggest the existence of Form Epsilon, much less processes for its preparation. The dictionary certainly does not cure this deficiency by stating that nitromethane is water soluble. Again, the unpredictable nature of polymorph generation precludes a *prima facie* case of obviousness.

In view of the foregoing amendments and remarks, Applicants respectfully submit that the present application is in condition for allowance. Early and favorable action by the Examiner is earnestly solicited. If any outstanding issues remain, the examiner is invited to telephone the undersigned at the telephone number indicated below to discuss the same.

Respectfully submitted,

KENYON & KENYON LLP

Date: February 2, 2007



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